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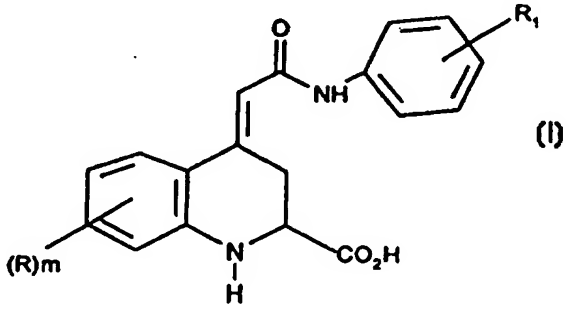
(54) Title: TETRAHYDROQUINOLINE DERIVATIVES AS EAA ANTAGONISTS

(57) Abstract

Compounds of formula (I) or a salt, or metabolically labile ester thereof wherein R represents a group selected from halogen, alkyl, alkoxy, amino, alkylamino, dialkylamino, hydroxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, SO_2R_2 or COR_2 wherein R_2 represents hydroxy, methoxy, amino, alkylamino or dialkylamino; m is zero or an integer 1 or 2; R_1 represents a group $(CH_2)nCN$, $-CH=CHR_3$, $(CH_2)nNHCOCH_2R_4$ or $O(CH_2)pNR_5R_6$; R_3 represents cyano or the group COR_7; R_4 represents alkoxy or a group $NHCOR_8$; R_5 and R_6 each represent independently hydrogen or alkyl, or R_5 and R_6 together with the nitrogen atom to which they are attached represent a heterocyclic group, or R_5 is hydrogen and R_6 is the group COR_9; R_7 represents an alkoxy, amino or hydroxyl group; R_8 represents a hydrogen atom or optionally substituted alkyl, alkoxy, aryl or heterocyclic group; R_9 is the group R_8 or the group $NR_{10}R_{11}$ wherein R_{10} represents hydrogen or alkyl group; R_{11} represents optionally substituted alkyl, aryl, heterocyclic or cycloalkyl group; n is zero or an integer from 1 to 4; p is an integer from 2 to 4, processes for their preparation and to their use in medicine.



(I)

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TETRAHYDROQUINOLINE DERIVATIVES AS EAA ANTAGONISTS

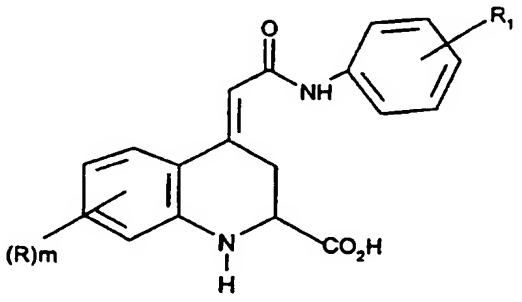
This invention relates to 1,2,3,4 tetrahydroquinoline derivatives, to processes for their preparation, to pharmaceutical compositions containing them and to their use in medicine. In particular, it relates to 1,2,3,4 tetrahydroquinoline derivatives which are potent and specific antagonists of excitatory amino acids.

EPA0386839 describes 1,2,3,4-tetrahydroquiolines possessing at least one substituent at the 4 position and an acidic group at the 2 position and which are specific antagonists of N-methyl-D-aspartate (NMDA) receptors.

Carling et al, Bioorganic and Medicinal Chemistry Letters Vol 13 pp 65-70 1993 teaches 4-substituted-2-carboxy tetrahydroquinolines having good *in vitro* affinity for the glycine modulatory site of the NMDA receptor complex but at best only weak *in vivo* activity. More particularly it teaches that such derivatives substituted at the 4 position by the group CH_2CO_2H or $CH_2CONHPh$ have little or no *in vivo* activity when administered systemically (ip).

We have found a novel group of 4 substituted 2-carboxy-tetrahydroquinoline derivatives which not only have a good *in vitro* affinity for the strychnine insensitive glycine binding site associated with the NMDA receptor complex but also good *in vivo* activity when administered systemically eg intravenously (iv).

Thus the present invention provides a compound of formula (I)



(I)

or a salt, or metabolically labile ester thereof wherein R represents a group selected from halogen, alkyl, alkoxy, amino, alkylamino, dialkylamino, hydroxy,

trifluoromethyl, trifluoromethoxy, nitro, cyano, SO_2R_2or COR_2 wherein R_2 represents hydroxy, methoxy, amino, alkylamino or dialkylamino; m is zero or an integer 1 or 2;

R_1 represents a group $(CH_2)nCN$, $-CH=CHR_3$, $(CH_2)nNHCOCH_2R_4$ or $O(CH_2)pNR_5R_6$; R_3 represents cyano or the group COR_7;

R_4 represents alkoxy or a group $NHCOR_8$;

R_5 and R_6 each represent independently hydrogen or alkyl, or

R_5 and R_6 together with the nitrogen atom to which they are attached represent a heterocyclic group, or R_5 is hydrogen and R_6 is the group COR_9;

R_7 represents an alkoxy, amino or hydroxyl group;

R_8 represents a hydrogen atom or optionally substituted alkyl, alkoxy, phenyl, heteroaryl or heterocyclic group;

R_9 is the group R_8 or the group $NR_{10}R_{11}$ wherein

R_{10} represents hydrogen or alkyl group;

R_{11} represents optionally substituted alkyl, phenyl, heteroaryl , heterocyclic or cycloalkyl group;

n is zero or an integer from 1 to 4; p is an integer from 2 to 4.

In compounds of formula (I) the exocyclic double bond is in the trans (E) configuration.

For use in medicine the salts of the compounds of formula (I) will be physiologically acceptable thereof. Other salts however may be useful in the preparation of the compounds of formula (I) or physiologically acceptable salts thereof. Therefore, unless otherwise stated, references to salts include both physiologically acceptable salts and non-physiologically acceptable salts of compounds of formula (I).

Suitable physiologically acceptable salts of compounds of the invention include base addition salts and where appropriate acid addition salts.

Suitable physiologically acceptable base addition salts of compounds of formula (I) include alkali metal or alkaline earth metal salts such as sodium, potassium, calcium, and magnesium, and ammonium salts, formed with amino acids (e.g. lysine and arginine) and organic bases (e.g. procaine, phenylbenzylamine, ethanolamine diethanolamine and N-methyl glucosamine).

The compounds of formula (I) and/or salts thereof may form solvates (e.g. hydrates) and the invention includes all such solvates.

Compounds of formula (I) and in particular the base addition salts thereof e.g. sodium salt have been found to have an advantageous profile of solubility in water.

The term alkyl as used herein as a group or part of a group refers to a straight or branched chain alkyl group containing from 1 to 4 carbon atom examples of such groups including methyl, ethyl, propyl, isopropyl, n-butyl, isobutyl, secondary butyl or tertiary butyl.

The term optionally substituted alkyl as used herein refers to an alkyl group as defined above and which is substituted by one or more hydroxy, carboxyl, and amino groups.

The term halogen refers to a fluorine, chlorine, bromine or iodine atom.

The term heteroaryl refers to a 5 or 6 membered heteroaryl group in which the 5-membered heteroaryl group contains 1 or 2 heteroatoms selected from oxygen sulphur or nitrogen and the 6-membered heteroaryl group containing 1 or 2 nitrogen atoms.

Examples of suitable heteroaryl groups include furanyl, thiophenyl, imidazolyl, thiazolyl, oxazolyl, pyridinyl, and pyrimidinyl.

The term optionally substituted phenyl refers to a phenyl group substituted with up to 3 substituents selected from halogen, C1-4 alkyl, C1-4 alkoxy, amino,alkylamino,hydroxy, trifluoromethyl, carboxyl or methoxycarbonyl.

The term cycloalkyl refers to a C_{3-7}cycloalkyl group which may optionally be substituted by 1 or 2 C_{1-4} alkyl groups e.g cyclopropyl, cyclobutyl,cyclopentyl, cyclohexyl cycloheptyl or 2-methylcyclohexyl.

The term optionally substituted heterocyclic group refers to 5-7 membered saturated heterocyclic groups containing one or two heteroatoms selected from oxygen, sulphur or nitrogen. Examples of suitable groups containing a single heteroatom include tetrahydropyranyl e.g. 4-tetrahydropyranyl, pyrrolidinyl e.g 2 or 3 pyrrolidinyl, piperidinyl e.g 4- or 3-piperidinyl and N-substituted derivatives therefore (e.g. N-alkyl such as .g. methyl or N-acyl such as N-alkanoyl e.g.

acetyl or N-alkoxycarbonyl e.g. ethoxycarbonyl), piperidino or pyrrolidino. Examples of suitable groups containing 2 heteroatoms include morpholino, thiomophlino or piperazino.

When R_5 and R_6 together with the nitrogen atom to which they are attached represent an heterocyclic group this is a saturated 5-7 membered ring optionally containing an additional heteroatom selected from oxygen, sulphur or nitrogen.

Examples of such groups include morpholino, 2,6 dimethylmorpholino, piperidino, pyrrolidino, piperazino or N-methylpiperazino.

The compounds of formula(I) possess at least one asymmetric carbon atom (namely the carbon atom occupying the 2 position of the 1, 2, 3, 4 tetrahydroquinoline ring system) and other asymmetric carbon atoms are possible in the groups R and R1. Also when R1 is the group $CH=CHR_3$, the group may exist in the cis or trans configuration or mixtures. It is to be understood that all stereoisomers including enantiomers, diastereoisomers and geometric isomers and mixtures thereof are encompassed within the scope of the present invention.

It will be appreciated that the compounds of formula (I) may be produced in vivo by metabolism of a suitable prodrug. Such prodrugs include for example physiologically acceptable metabolically labile esters of compounds of the general formula (I). These may be formed by esterification, for example of any of the carboxylic acid groups in the parent compound of general formula (I) with, where appropriate, prior protection of any other reactive groups present in the molecule, followed by deprotection if required. Examples of such metabolically labile esters include C_{1-4}alkyl esters e.g. methyl or ethyl esters, substituted or unsubstituted aminoalkyl esters (e.g. aminoethyl, 2-(N,N- diethylamino) ethyl, or 2-(4-morpholino)ethyl esters or acyloxyalkyl esters such as, acyloxymethyl or 1-acyloxyethyl e.g. pivaloyloxymethyl, 1-pivaloyloxyethyl, acetoxymethyl, 1-acetoxyethyl, 1-(1-methoxy-1-methyl)ethylcarbonyloxyethyl, 1- benzoyloxyethyl, isopropoxycarbonyloxymethyl, 1-isopropoxycarbonyloxyethyl, cyclohexylcarbonyloxymethyl, 1-cyclohexylcarbonyloxyethyl ester, cyclohexyloxycarbonyloxymethyl, 1-cyclohexyloxycarbonyloxyethyl, 1-(4-

tetrahydropyranyloxy)carbonyloxyethyl or 1-(4-tetrahydropyranyl)carbonyloxyethyl.

For compounds of formula (I) m is conveniently 1 or 2 and within these compounds those wherein R is at the 5 and/or 7 position are preferred.

The group R is conveniently a halogen atom, such as bromine or chlorine and preferably is a chlorine atom.
A preferred group of compounds of formula (I) are those wherein m is 2 and R which is at the 5 and 7 position is bromine or more particularly chlorine.

When R_3 is the group COR_7, R_7 is conveniently hydroxyl, amino or C_{1-4}alkoxy e.g. methoxy, ethoxy, propoxy, butoxy and t-butoxy.

When R_4 is the group $NHCOR_8$, R_8 is conveniently hydrogen or C_{1-4}alkyl e.g. methyl, ethyl,isopropyl, butyl or isobutyl. When R_1 is the group $O(CH_2)pNR_5R_6$. Conveniently R_5 and R_6 each represent hydrogen or NR_5R_6 represents a morpholino group, or R5 represents hydrogen and R_6 represents COR_9 wherein R_9 is hydrogen or C_{1-4}alkyl or the group NH_2.
n is conveniently zero, 1 or 2;
p is conveniently 2.

The group R_1 may be in the 2, 3 or 4 position in the phenyl ring and is conveniently at the 3 or 4 position. Preferably R_1 is at the 4 position.

A preferred class of compounds are those wherein R_1 is the group $(CH_2)nCN$ (eg. CH_2CN), $-CH=CHR_3$ wherein R_3 is cyano or COR_7 (wherein R_7 is C_{1-4} alkoxy(e.g. t-butoxy) or amino), $(CH_2)nNHCOCH_2R4$ (wherein R_4 is alkoxy e.g. methoxy or $NHCOR_8$ wherein R_8 is hydrogen or C_{1-4}alkyl (e.g. isopropyl)) or $O(CH_2)pNR_5R_6$ wherein R_5 and R_6 are hydrogen (e.g. aminoethoxy) or NR_5R_6 represents morpholino (e.g. morpholino ethoxy) or R_5 represents hydrogen and R_6 is COR_9 wherein R_9 is hydrogen or C_{1-4}alkyl e.g isopropyl. Within this class of compounds n is zero, 1 or 2 and more preferably 1; p is 2, 3 or 4 and more preferably 2.

A particularly preferred class of compounds are those wherein R_1 is the group CH_2CN, $-CH=CHR_3$ (wherein R_3 is C_{1-4}alkoxycarbonyl eg butoxycarbonyl, carbamoyl or cyano), $(CH_2)_nNHCOCH_2R_4$ (wherein n is zero and R_4 is C_{1-4}alkoxy, eg methoxy or $NHCOR_8$ wherein R_8 is C_{1-4}alkyl eg isopropyl), eg R_1 is 2-methoxyacetylamino or isobutyrylamino-methylcarbonylamino, or R_1 is $O(CH_2)pNR_5R_6$ (wherein p is 2, R_5 is hydrogen and R_8 is COR_9 wherein R_9 is C_{1-4}alkyl eg isopropyl, or NR_5R_6 represents a morpholino group) eg R_1 is 2-isobutyryl aminoethoxy or 2-morpholino-4-ylethoxy.

Specific preferred compounds of the invention include:

(±) (E) 5,7- Dichloro- 4-[4-(2-methoxy-acetylamino)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
(±) (+,-) (E) 5,7- Dichloro- 4-[4-(2-isobutyrylamino-methylcarbonylamino)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
and physiologically acceptable salts e.g. sodium salt , metabolically labile esters or enantiomers thereof.

Further specific preferred compounds of the invention include:

(±) (E) 5,7- Dichloro- 4-(4-cyanomethyl-phenylcarbamoylmethylene)-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
(±) (E,E) 5,7- Dichloro- 4-[4-(2-cyano-vinyl)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
(±) (E,E) 4-[4-(2-tert-butoxycarbonyl-vinyl)-phenylcarbamoylmethylene]-5,7-dichloro-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
(±) (E,E) 4-[4-(2-carbamoyl-vinyl)-phenylcarbamoylmethylene]-5,7- dichloro-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
(±) (E) 5,7- Dichloro- 4-[4-(2-isobutyrylamino-ethoxy)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
(±) (E) 5,7- Dichloro- 4-[4-(2-morpholin-4-yl-ethoxy)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
and physiologically acceptable salts e.g. sodium salt , metabolically labile esters or enantiomers thereof.

The compounds of formula (I) and/or physiologically acceptable salts thereof are excitatory amino acid antagonists. More particularly they are potent antagonists at the strychnine insensitive glycine binding site associated with the NMDA receptor complex. As such they are potent antagonists of the NMDA receptor complex. These compounds are therefore useful in the treatment or prevention of neurotoxic damage or neurodegenerative diseases. Thus the compounds are useful for the treatment of neurotoxic injury which follows cerebral stroke, thromboembolic stroke, hemorrhagic stroke, cerebral ischemia, cerebral vasospam, hypoglycemia, anaesia, hypoxia, anoxia, perinatal asphyxia cardiac arrest. The compounds are also useful in the treatment of chronic neurodegenerative diseases such as; Huntingdon's disease, Alzheimer's senile dementia, amyotrophic lateral sclerosis, Glutaric Acidaemia type, multi-infarct dementia, status epilecticus, contusive injuries (e.g. spinal cord injury and head injury), viral infection induced neurodegeration (e.g. AIDS, encephalopaties), Down syndrome, epilepsy, schizophrenia, depression, anxiety, pain, migraine, headaches including cluster headaches and or tension headaches, neurogenic bladder, irritative bladder disturbances, drug dependency, including withdrawal symptoms from alcohol, cocaine, opiates, nicotine, benzodiazepine, and emesis.

The potent and selective action of the compound of the invention at the strychnine- insensitive glycine binding site present on the NMDA receptor complex may be readily determined using conventional test procedures. Thus the ability to bind at the strychnine insensitive glycine binding site was determined using the procedure of Kishimoto H et al. J Neurochem 1981, 37 1015-1024. The selectivity of the action of compounds of the invention for the strychnine insensitive glycine site was confirmed in studies at other ionotropic known excitatory amino acid receptors. Thus compounds of the invention were found to show little or no affinity for the kainic acid (kainate) receptor, a-amino-3-hydroxy-5-methyl-4-isoxazole-proprionic acid (AMPA) receptor or at the NMDA binding site.

Compounds of the invention have also been found to inhibit NMDA induced convulsions in mice using the procedure Chiamulera C et al. Psychopharmacology (1990) 102, 551-552.

The ability of compounds of the invention to inhibit pain may be demonstrated in conventional analgesic screens such as those described by J J Bennett and J K Xue, Pain 1988,41,87-107.

The invention therefore provides for the use of a compound of formula (I) and/or physiologically acceptable salt or metabolically labile ester thereof for use in therapy and in particular use as medicine for antagonising the effects of excitatory amino acids upon the NMDA receptor complex.

The invention also provides for the use of a compound of formula (I) and/or a physiologically acceptable salt or metabolically labile ester thereof for the manufacture of a medicament for antagonising the effects of excitatory amino acids upon the NMDA receptor complex.

According to a further aspect, the invention also provides for a method for antagonising the effects of excitatory amino acids upon the NMDA receptor complex, comprising administering to a patient in need thereof an antagonistic amount of a compound of formula (I) and/or a physiologically acceptable salt or metabolically labile ester thereof.

It will be appreciated by those skilled in the art that reference herein to treatment extends to prophylaxis as well as the treatment of established diseases or symptoms.

It will further be appreciated that the amount of a compound of the invention required for use in treatment will vary with the nature of the condition being treated, the route of administration and the age and the condition of the patient and will be ultimately at the discretion of the attendant physician. In general however doses employed for adult human treatment will typically be in the range of 2 to 800mg per day, dependent upon the route of administration.
Thus for parenteral administration a daily dose will typically be in the range 20-100mg, preferably 60-80mg per day. For oral administration a daily dose will typically be within the range 200-800mg, e.g. 400-600mg per day.

The desired dose may conveniently be presented in a single dose or as divided doses administered at appropriate intervals, for example as two, three, four or more sub-doses per day.

While it is possible that, for use in therapy, a compound of the invention may be administered as the raw chemical, it is preferable to present the active ingredient as a pharmaceutical formulation.

The invention thus further provides a pharmaceutical formulation comprising a compound of formula (I) or a pharmaceutically acceptable salt or metabolically labile ester thereof together with one or more pharmaceutically acceptable carriers thereof and, optionally, other therapeutic and/or prophylactic ingredients. The carrier(s) must be 'acceptable' in the sense of being compatible with the other ingredients of the formulation and not deleterious to the recipient thereof.

The compositions of the invention include those in a form especially formulated for oral, buccal, parenteral, inhalation or insufflation, implant, or rectal administration. Parenteral administration is preferred.

Tablets and capsules for oral administration may contain conventional excipients such as binding agents, for example, syrup, accacia, gelatin, sorbitol, tragacanth, mucilage of starch or polyvinylpyrrolidone; fillers, for example, lactose, sugar, microcrystalline cellulose, maize-starch, calcium phosphate or sorbitol; lubricants, for example, magnesium stearate, stearic acid, talc, polyethylene glycol or silica; disintegrants, for example, potato starch or sodium starch glycollate, or wetting agents such as sodium lauryl sulphate. The tablets may be coated according to methods well known in the art. Oral liquid preparations may be in the form of, for example, aqueous or oily suspensions, solutions emulsions, syrups or elixirs, or may be presented as a dry product for constitution with water or other suitable vehicle before use. Such liquid preparations may contain conventional additives such as suspending agents, for example, sorbitol syrup, methyl cellulose, glucose/sugar syrup, gelatin, hydroxyethylcellulose, carboxymethyl cellulose, aluminium stearate gel or hydrogenated edible fats; emulsifying agents, for example, lecithin, sorbitan mono-oleate or acacia; non-aqueous vehicles (which may include edible oils), for example, almond oil, fractionated coconut oil, oily esters, propylene glycol or thyl alcohol; solubilizers such as surfactants for

example polysorbates or oth r agents such as cyclodextrins; and preservatives, for example, methyl or propyl p- hydroxybenzoates or ascorbic acid. The compositions may also be formulated as suppositories, e.g. containing conventional suppository bases such as cocoa butter or other glycerides.

For buccal administration the composition may take the form of tablets or lozenges formulated in conventional manner.

The composition according to the invention may be formulated for parenteral administration by injection or continuous infusion. Formulations for injection may be presented in unit dose form in ampoules, or in multi-dose containers with an added preservative. The compositions may take such forms as suspensions, solutions, or emulsions in oily or aqueous vehicles, and may contain formulatory agents such as suspending, stabilising and/or dispersing agents. Alternatively the active ingredient may be in powder form for constitution with a suitable vehicle, e.g. sterile, pyrogen-free water, before use.

For administration by inhalation the compounds according to the invention are conveniently delivered in the form of an aerosol spray presentation from pressurised packs, with the use of a suitable propellant, such as dichlorodifluoromethane, tirchlorofluoromethane, dichloro-tetrafluoroethane, carbon dioxide or other suitable propellants, such as dichlorodifluoromethane, trichlorofluoromethane, dichloro-tetrafluoroethane, carbon dioxide or other suitable gases, or from a nebuliser. In the case of a pressurised aerosol the dosage unit may be determined by providing a valve to deliver a metered amount.

Alternatively, for administration by inhalation or insufflation, the compounds according to the invention may take the form of a dry powder composition, for example a powder mix of the compound and a suitable carrier such as lactose or starch. The powder composition may be presented in unit dosage form in, for example, capsules or cartridges of e.g. gelatin, or blister packs from which the powder may be administered with the aid of an inhaler or insufflator.

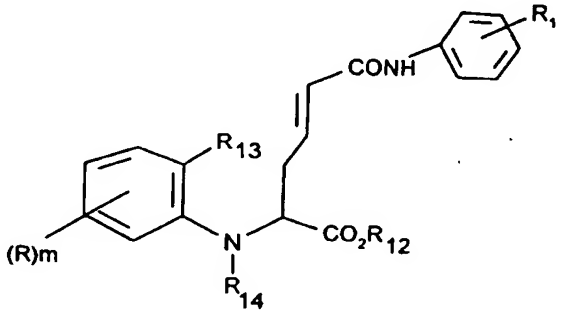
The composition according to the invention may also be formulated as a depot preparation. Such long acting formulations may be administered by implantation

(for example subcutaneously or intramuscularly) or by intramuscular injection. Thus for example, the compounds of the invention may be formulated with suitable polymeric or hydrophobic materials (for example as an emulsion in an acceptable oil) or ion exchange resins, or as sparingly soluble derivatives, for example, as a sparingly soluble salt.

The compositions according to the invention may contain between 0.1 - 99% of the active ingredient, conveniently from 30- 95% for tablets and capsules and 3-50% for liquid preparations.

Compounds of general formula (I) and salts thereof may be prepared by the general methods outlined hereinafter. In the following description, the groups R, m, R_1 are as defined for the compounds of formula (I) unless otherwise stated.

Compounds of formula (I) may be prepared by the cyclisation of a compound of formula (II) in which R_{12} is a carboxylic protecting group, R_{13} represents a bromine or iodine atom, R_{14} represents hydrogen or a nitrogen protecting group and R_1 has the meanings defined in formula(I) or a protected derivative thereof.



(II)

In one embodiment of this process the reaction may be carried out using a catalytic amount of a Palladium (O) complex such as tetrakis(triphenylphosphine)palladium and a suitable organic base such as trialkylamine e.g triethylamine or inorganic base, e.g. potassium carbonate.
The reaction is conveniently carried out in an aprotic solvent such as acetonitrile or dimethylformamide at a temperature with the range of 60°C to 150°C followed, where necessary or desired, by subsequent removal of the carboxyl protecting group R_{12} and any protecting group R_{14}.

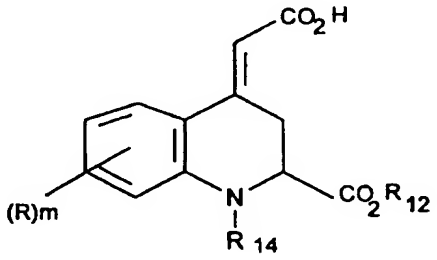
In a further embodiment of the process the reaction is carried out using a catalytic amount of a Pd(II) salt such as: palladium acetate, in the presence of a suitable organic base such as a trialkyl amine e.g. triethylamine and a triarylphosphine such as triphenylphosphine.

The reaction is carried out in an aprotic solvent such as acetonitrile or dimethylformamide and preferably with heating, where necessary or desired, by subsequent removal of the carboxyl protecting group R_{12} and any protecting group R_{14}.

Suitable carboxyl protecting groups R_{12} for use in this reaction include alkyl, trichloroalkyl, trialkylsilylalkyl, or arylmethyl groups such as benzyl, nitrobenzyl or trityl.

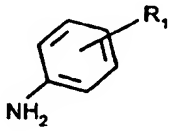
When R_{14} is nitrogen protecting examples of suitable groups include alkoxycarbonyl e.g. t-butoxycarbonyl, arylsulphonyl e.g. phenysulphonyl or 2-trimethylsilylethoxymethyl.

In a further process of the invention compounds of formula(I), may be prepared by reaction of an activated derivative of the carboxylic acid (III) in which R_{12} is a carboxyl protecting group and R_{14} is hydrogen or a nitrogen protecting group as defined in formula (II)



(III)

with the amine(IV)



(IV)

wherein R1 has the meaning defined in formula(I) or are protected derivative thereof, followed where necessary by subsequent removal of the carboxyl protecting group R_{12} and any nitrogen protecting group R_{14}.

Suitable activated derivatives of the carboxyl group include the corresponding acyl halide, mixed anhydride, activated ester such as a thioester or the derivative formed between the carboxylic acid group and a coupling agent such as that used in peptide chemistry, for example carbonyl diimidazole or a diimide such as dicyclohexylcarbodiimide.

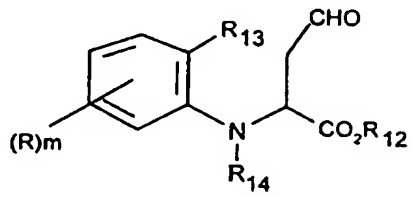
The reaction is preferably carried out in an aprotic solvent such as a hydrocarbon, a halohydrocarbon, such as dichloromethane or an ether such as tetrahydrofuran.

Suitable carboxyl protecting groups R_{12} for use in this reaction include alkyl, trichloroalkyl, trialkylsilylalkyl, or arylmethyl groups such as benzyl, nitrobenzyl or trityl.

When R_{14} is nitrogen protecting examples of suitable groups include alkoxycarbonyl e.g. t-butoxycarbonyl, arylsulphonyl e.g. phenysulphonyl or 2-trimethylsilylethoxymethyl

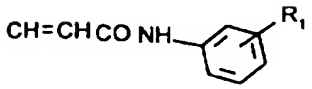
The activated derivatives of the carboxylic acid (III) may be prepared by conventional means. Particularly suitable activated derivatives for use in this reaction are thioesters such as that derived from pyridine-2-thiol. These esters may conveniently be prepared by treating the carboxylic acid (III) with 2,2'-dithiopyridine and triphenylphosphine in a suitable aprotic solvent such as an ether e.g. tetrahydrofuran, a halohydrocarbon e.g. dichloromethane, an amide e.g. N,N-dimethylformamide or acetonitrile.

Compounds of formula (II) may be prepared from compound of formula (V) in which R_{12} is a carboxyl protecting group and R_{14} is hydrogen or a nitrogen protecting group as defined in formula (II) and R_{13} represents a bromine or iodine atom



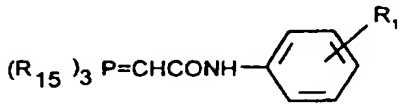
(V)

by rection with an appropriate phosphorus reagent capable of converting the group CHO into the group :



followed, where necessary or desired, by removal of the carboxyl protecting group R_{12}.and nitrogen protecting group R_{14}

In one embodiment of this process the reaction may be carried out using a phoshorus ylide of formula (VI)

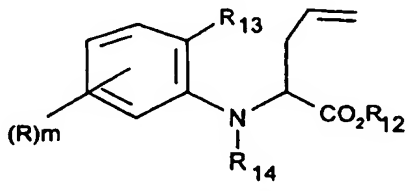


(VI)

wherein R_{15} is an alkyl or phenyl group and R_1 has the meanings defined in formula(I) or a protected derivative thereof.

The reaction is carried out in an aprotic solvent such as acetonitrile or dimethylformamide at a temperature ranging from -10°C to the reflux temperature of the solvent.

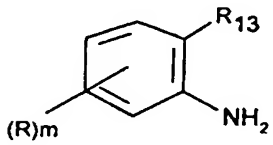
Compounds of formula (V) may be prepared by ozonization of the allyl compound of formula (VII) in which R_{12} is a carboxyl protecting group, R_{14} is hydrogen or a nitrogen protecting group as defined above and R_{13} represents a bromine or iodine atom.



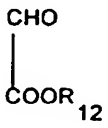
(VII)

The reaction may be effected by passing a stream of ozone into a solution of compound of formula (VII) in the presence of dimethyl sulphide or triphenylphosphine in a suitable solvent such as halohydrocarbon e.g dichloromethane at low temperature e.g -78°C.

Compounds of formula (VII) wherein R_{14} is hydrogen atom and R_{12} is carboxyl protecting group as defined above may be prepared by reaction of the amine(VIII) wherein R_{13} represents a bromine or iodine atom with the aldehyde (IX) in which R_{12} is carboxyl protecting group



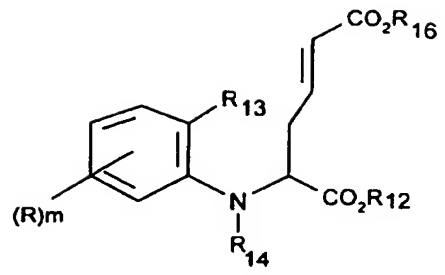
(VIII)



(IX)

followed by addition of allyltributyltin in the presence of Lewis acid such as titanium(IV) chloride or boron trifluoride etherate.The reaction conveniently takes place in a solvent such as hydrocarbon e.g toluene or halogenated hydrocarbon e.g. dichloromethane at a temperature ranging from -78°C to room temperature.
Compounds of formula (VII) in which R_{14} is nitrogen protecting group and R_{12} is carboxyl protecting group as defined above may be prepared from the compound of formula(VII) wherein R_{14} represents hydrogen atom using conventional procedure for preparing such protected nitrogen atom.

Compounds of formula (III) may be prepared by the cyclisation of a compound of formula (X) in which R_{12} is a carboxylic protecting group, R_{13} represents a bromine or iodine atom, R_{14} represents hydrogen or a nitrogen protecting group as defined above, and R_{16} represents a suitable carboxyl protecting group such as a t-butyl group

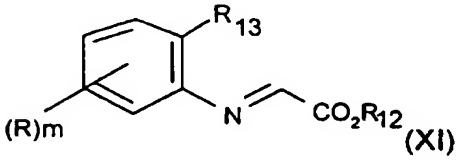


(X)

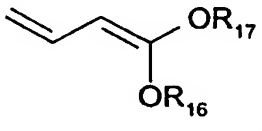
using similar reaction conditions for those described above for the reaction of compounds of formula (II), followed by removal of the carboxyl protecting group R16 and where necessary or desired by removal of the nitrogen protecting group R_{14} The carboyl protecting group may be removed by conventional procedures. Thus when R_{16} is a t-butyl group it may be removed by reaction with formic acid.

Compounds of formula (X) may be prepared from compound of formula(V) and a phosphourus ylide $(R_{15})_3P=CHCO_2R_{16}$ in which R_{15} has the meaning defined in formula (VI) and R_{16} is as defined above, using similar reaction condition for those described above for the reaction of (V) with compound of formula (VI).

In a further process of the invention compounds of formula(X) may be prepared by reaction of the imino compound(XI), in which R_{12} is a carboxylic protecting group, R_{13} represents a bromine or iodine atom , with silane derivatives (XII)



(XI)



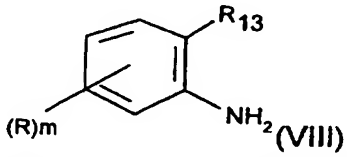
(XII)

wherein R17 is a trialkylsilyl group such as tri(C1-4)alkyl group. Example of suitable trialkylsilyl groups include trimethylsilyl and ter-butyldimethylsilyl and R_{16} represents a suitable protecting group such as t butyl group, in the presence of Lewis acid such as stannic chloride or stannic bromide.

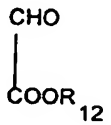
The reaction is conveniently carried out at temperature ranging from -78°C. to room temperature in an aprotic solvent such as halohydrocarbons i.e

dichloromethane, or aromatic hydrocarbons such as toluene, chlorobenzene or fluorobenzene

Compounds of formula(XI) may be prepared by reaction of compounds of formula(VIII) and (IX). wherein R_{13} represents a bromine or iodine atom with the aldehyde (IX) in which R_{12} is carboxyl protecting group



(VIII)



(IX)

The reaction conveniently takes places in a solvent such as hydrocarbon e.g toluene at reflux temperature in the presence of a drying agent such as magnesium sulphate or sodium sulphate.

Compounds of formula (IV),(VI),(VIII) (IX) and (XII) are either known compounds or may be prepared by analogous methods to those used for known compounds.

Specific enantiomers of the compounds of formula(I) may be obtained by resolution of the racemic compounds using conventional procedures such as salts formation with a suitably optically active amine i.e. (R)-α-phenylethylamine, (S) α-phenylethylamine, brucine, cinconidine, quinine, followed by separation of the two diastereoisomer salts obtained and regeneration of the free acid. The two diastereoisomeric salts may be conveniently separated by conventional means such as fractional crystallisation.

Alternatively the required enantiomer may be obtained from racemic compounds of formula(I) by use of chiral HPLC procedures.

In a further process of the invention the required enantiomer may be prepared by esterification of a compound of formula(I) with a suitable chiral alcohol, separating the resultant diastereoisomeric esters by conventional means e.g. chromatography, followed by hydrolysis of the required single diastereomeric ester.

Suitable chiral alcohols for use in the process include S(+)-indanol, S(+)-methyl mandelate, S(-) methyl lactate or R(+) t-butyl lactate.

The diastereoisomeric esters of a compound of formula (I) may be prepared by conventional means such as reaction of the chiral alcohol with an activated derivative of a compound of formula (I) in an aprotic solvent such as ether e.g. tetrahydrofuran.
The activated derivative of a compound of formula(I) may be prepared from a compound of formula(I) using conventional means for preparing activated derivatives of a carboxylic acid groups such as those conveniently used in peptide synthesis.

A convenient method of preparing the diastereisomeric esters of a compound of formula(I) is to prepare the activated derivative of a compound of formula(I) in the presence of the chiral alcohol.

Thus for example a compound of formula(I) may be treated with the Mitsunobu combination of reagents, i.e. a dialkylazo-dicarboxylate such as diethylazodicarboxylate and a triarylphosphine e.g. triphenylphosphine in the presence of the chiral alcohol.

The reaction conveniently takes place in the presence of a suitable solvent such as an ether (e.g. diethylether or tetrahydrofuran), a halohydrocarbon (e.g. diethylether or tetrahydrofuran), a halohydrocarbon (e.g. dichloromethane) or a nitrile (e.g. acetonitrile) or a mixture thereof at a temperature ranging from 0-30°.

The required single diastereoisomeric ester of a compound of formula(I) substantially free of the other diastereoisomers may be obtained from the mixture thereof by conventional means, for example by the use of conventional chromatographic procedures such as preparative hplc or by fractional crystallization.

The required enantiomer may be prepared from the corresponding single diastereoisomeric ester of a compound of formula(I) by hydrolysis e.g. alkaline hydrolysis. Thus for example the hydrolysis may be carried using an alkali metal

hydroxide e.g. sodium hydroxide or lithium hydroxide in a solvent such as an ether e.g. tetrahydrofuran and water.

In any of the above reactions the carboxyl protecting group may be removed by conventional procedures known for removing such groups. Thus compounds where R_{12} is a benzyl group, this may be removed by hydrolysis using an alkali metal hydroxide e.g. lithium hydroxide or sodium hydroxide in a suitable solvent such as ethanol or isopropanol, water or mixtures thereof, followed, where desired or necessary, by that addition of a suitable acid e.g. hydrochloric acid to give the corresponding free carboxylic acid.

In any of the above reactions the nitrogen protecting group may be removed by conventional procedures known for removing such groups, for example by acid or base hydrolysis. Thus when R_{14} is alkoxycarbonyl e.g. t-butoxycarbonyl or phenylsulphonyl it may be removed by alkaline hydrolysis using for example lithium hydroxide in a suitable solvent such as tetrahydrofuran or an alkanol e.g. isopropanol. Alternatively the alkoxycarbonyl group may be removed by acid hydrolysis. When R_{16} is t butyl group this may be removed by hydrolysis using organic acids eg formic acid.

Physiologically acceptable salts of compounds of formula (I) may be prepared by treating the corresponding acid with an appropriate base in a suitable solvent. For example alkali and alkaline metal salts may be prepared from an alkali or alkaline metal hydroxide, or the corresponding carbonate or bicarbonate thereof. Alternatively alkali or alkaline metal salts may be prepared by direct hydrolysis of carboxyl protected derivatives of compounds of formula (I) with the appropriate alkali or alkaline metal hydroxide.

Metabolically labile esters of compounds of formula (I) may be prepared by esterification of the carboxylic acid group or a salt thereof or by trans esterfication using conventional procedures. Thus, for example, acyloxyalkyl esters may be prepared by reacting the free carboxylic acid or a salt thereof with the appropriate acyloxylalkyl halide in a suitable solvent such as dimethylformamide. For the esterifcation of the free carboxyl group this reaction is preferably carried out in the presence of a quaternary ammonium halide such as t trabutylammonium chloride or benzyltriethylammonium chloride.

Aminoalkyl esters may be prepared by transesterification of a corresponding alkyl ester e.g. methyl or ethyl ester by reaction with the corresponding aminoalkanol at an elevated temperature e.g. 50-150°.

In order that the invention may be more fully understood the following examples are given by way of illustration only.

In the Intermediates and Examples unless otherwise stated:

Melting points (m.p.) were determined on a Gallenkamp m.p. apparatus and are uncorrected. All temperatures refers to ^0C. Infrared spectra were measured on a FT-IR instrument. Proton Magnetic Resonance (^1H-NMR) spectra were recorded at 400 MHz, chemical shifts are reported in ppm downfield (d) from Me_4Si, used as internal standard , and are assigned as singlets (s), doublets (d), doublets of doublets (dd), triplets (t), quartets (q) or multiplets (m). Column chromathography was carrier out over silica gel (Merck AG Darmstaadt, Germany). The following abbreviations are used in text: EA = ethyl acetate, CH = cyclohexane, DCM = dichloromethane.THF= tetrahydrofuran ,Tlc refers to thin layer chromatography on silica plates. Solution were dried over anhydrous sodium sulphate; r.t. refers to room temperature.

Intermediate 1

4,6-Chloro-1-iodo-2-nitrobenzene

2-Nitro-4,6-dichloroaniline (5g) was dissolved in a 12N solution of H_2SO_4(20ml) and cooled at 0^o. Then, a solution of $NaNO_2$ (2.15g) in H_2SO_4 (5ml) was carefully added followed by polyphosphoric acid (40ml). The reaction mixture was allowed to warm at room temperature and stirred for 3hrs. Then, the solution was poured into crushed ice and urea was added until gas evolution ceased.The resulting mixture was treated with an aqueous solution of potassium iodide (5.6g) and heated at 70° for 2hrs. The reaction mixture was diluted with a 10% solution of sodium hydroxide (40ml), extracted with ethyl acetate (3x40ml), washed with brine (3x25ml), dried and concentrated under vacuum. The title compound was obtained as a red oil (7.5g).

^{1}H-NMR ($CDCl_3$): 7.67 (1H, d); 7.54 (1H, d).
I.R.(nujol): 1454cm^{-1}, 1350cm^{-1}.

Intermediate 2
2-Iodo-3,5-dichloroaniline

To a solution of Intermediate 1 (4g) in 95% ethanol (35ml) glacial acetic acid (35ml) and iron (2.8g) was added. The reaction mixture was heated at 100° for 1h diluted with a saturated solution of sodium hydrogen carbonate and extracted with ethyl acetate (3X20ml). The organic layer was washed with brine (2x20ml), dried, concentrated under vacuum to give the title compound as brown solid (2.9g).
IR (nujol): ν_{max} (cm^{-1}) = 3491(NH2); 3103 (NH2); 1614 (C=C).

Intermediate 3
(+/-) 2-(3,5-dichloro-2-iodo-phenylamino)-pent-4-enoic acid benzyl ester

To a solution of intermediate 2 (1.5g) in dry toluene (20ml) benzylglyoxylate (1.070g) and Na_2SO_4 were added (2.5g). The mixture was refluxed overnight. After filtration the resulting solution was concentrated under vacuum to a brown oil, which was then taken up with dry dichloromethane (40ml). After cooling to -78°, $TiCl_4$ (0.57ml) was slowly added with a syringe and stirring continued for 5 min. The solution was then allowed to warm to room temperature over 30min by removing the dry ice/acetone bath, then cooled again to -78° and tributylallyltin (1.94 ml) added. After 1 hour the reaction was stopped by pouring it into a saturated solution of NH_4Cl (100ml). The aqueous phase was extracted with ethyl acetate (2x200ml) and the combined organic fractions washed with HCl (3N, 2x70ml) brine (50ml) and dried. Final purification by column chromatography (CH/EA 95/5) gave the title compound (1.05g) as a yellow oil.

^{1}H-NMR ($CDCl_3$): 7.4 - 7.3 (3H, m); 6.87 (1H, d); 6.27 (1H, d); 5.72 (1H, m); 5.22 - 5.16 (2H, m); 5.19 (2H, s); 5.14 (1H, d); 4.16 (1H, t); 2.65 (2H,m).
I.R. (neat): 3371cm^{-1}; 1744cm^{-1}; 1572cm^{-1}

Intermediat 4

(+/-) 2-(3.5-Dichloro-2-iodo-phenylamino)-4-oxo-butyric acid b nzyl ster

Intermediate 3 (1.0g) was dissolved in dry dichloromethane (40ml) and the resulting solution cooled to -78° with a dry ice/acetone bath. Ozone was bubbled through it until a brick-red color appeared (approx 20min), then triphenylphosphine (0.82g) was added and the cooling bath removed. After the warm-up was complete the solution was concentrated to dryness and then purified by column chromatography (CH/EA 80/20) to give the title compound (0.745g) as a colorless oil.

^{1}H-NMR ($CDCl_3$): 9.77 (1H, s); 7.36 - 7.28 (5H, m); 6.91 (1H, d); 6.40 (1H,d); 5.34 (1H, d); 5.20 (2H, s); 4.50 (1H, dt); 3.09 (2H, d).
I.R. (nujol): 3371cm^{-1}; 1738cm^{-1}, 1732cm^{-1}

Intermediate 5
(+/-)(E)-2-(3,5-dichloro-2-iodo-phenylamino)-hex-2-endioic acid-6-benzyl-1-tert-butylester

Intermediate 4 (8.2g) was dissolved in dry toluene (200ml), (tert-butoxycarbonyl methylene) triphenylphosphorane was then added and the mixture was stirred at 100°C for 2h. The solvent was removed under vacuum and the crude product was purified by flash-chromatography (CH/EA 95/5) to give the title compound (6.00g) as a white solid. m.p. 95-96°

^{1}H-NMR (d_6-acetone): 7.4-7.3 (m,5H); 6.92 (d,1H); 6.82 (dt,1H); 6.67 (d,1H), 5.88 (dt,1H); 5.40 (d,1H); 5.24 (s,2H); 4.66 (dt,1H); 3.0-2.8 (m,2H); 1.5 (s,9H)

Intermediate 6
(+/-)(E)-5-(3,5-dichloro-2-iodo-phenylamino)-hex-2-endioic acid 6-benzyl ester

Intermediate 5 (0.2g) was dissolved in formic acid (5ml) and stirred at room temperature for 24 h. The reaction mixture was then evaporated to dryness to give the title compound (0.180g).

^{1}H NMR (DMSO): 12.3 (bs, 1H); 7.4-7.3 (m, 5H); 7.01 (d, 1H); 6.73 (dt, 1H); 6.66 (d, 1H); 5.87 (d, 1H); 5.37 (d, 1H); 5.18 (s, 2H); 4.73 (dt, 1H); 2.81 (t, 1H).

Intermediate 7

(+/-)-(E,E)-5-[4-(2-cyano-vinyl)-phenylcarbamoyl]-2-(3,5-Dichloro-2-iodo-phenylamino)-penten-4-enoic acid benzyl ester

Intermediate 6 (0.2 g) was dissolved in dry THF (3 ml) at -20° and PCl_5 (0.1 g) was added portionwise. The mixture was stirred for 1 h at -20°, then pyridine (0.046 ml) and 3-(4-amino-phenyl)-acrylamide (0.074 g) were added. The temperature was allowed to increase slowly to room temperature over 2 h. After an additional 2 h, the solution was taken up with ethyl acetate, washed twice with 3N HCl, then with water and brine. After drying and filtration the solution was concentrated to give a crude product, which was purified by column chromatography (CH/EA 7/3) to give the title compound (0.09 g) as an 8/2 mixture with a non-identifiable isomer at one of the two double bonds. **mp:** 132-134°C

NMR: ^{1}H d ($CDCl_3$) 9.46 (1H, bs), 7.79 (2H, d), 7.62 (2H, d), 7.50 (1H, d), 7.5-7.3 (5H, m), 7.0-6.9 (2H, m), 6.67 (1H, d), 6.25 (1H, d), 6.17 (1H, d), 5.43 (1H, d), 5.26 (2H, s), 4.69 (1H, m), 2.93 (2H, m).
IR: ($CDCl_3$) ν_{max} (cm^{-1}) 2210, 1738.

Intermediate 8
(+/-)(E)-5,7-dichloro-4-tert-butoxycarbonylmethylene-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid benzyl ester

Intermediate 5 (6.5g) was dissolved in dry dimethylformamide (150ml). To this solution, tetrakis(triphenylphosphine)palladium (0.65g) and triethylamine (9.15ml) were added and the reaction mixture was heated to 100° for 1 h under nitrogen atmosphere. The reaction mixture was then cooled to room temperature, diluted with ethyl acetate (250ml), washed with a saturated solution of aqueous NH_4Cl (100ml) and with brine (3x100ml). The organic layer was separated, dried, filtered and evaporated under vacuum. The crude product was purified by flash chromatography (EA/CH 1/9) to give the title compound (4g) as a white solid.

^{1}H -NMR(DMSO): 7.44-7.3 (m, 5H); 6.77 (d, 1H); 6.70 (d, 1H); 6.47 (bs, 1H); 6.45 (s, 1H); 5.21 (d, 1H); 5.02 (d, 1H); 4.40 (td, 1H); 3.98 (dd, 1H); 3.11 (ddd, 1H); 1.5 (s, 9H).

Intermediate 9
(+/-)(E)-5,7 -dichloro-4-carboxymethylene-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid benzyl ester

Intermediate 8 (0.96g) was suspended in formic acid (40ml) and stirred at room temperature for 2 hours. The solvent was removed under vacuum, then the solid was suspended in ether and then concentrated again to dryness to give the title compound (0.86 mg) as a white solid. m.p. 210-212°.

^{1}H-NMR (d_6-acetone): 11.2-10.6 (bs,1H); 7.4-7.3 (m,5H); 6.78 (d,1H); 6.71 (d,1H); 6.57 (s,1H); 6.49 (bs,1H); 5.18 (d,1H), 5.03 (d,1H); 4.41 (t,1H); 4.05-4 (m,1H); 3.14 (ddd,1H)
I.R.(Nujol): 3373cm^{-1}; 1726cm^{-1}; 1688cm^{-1}; 1614cm^{-1}

Intermediate 10
(+/-)(E)-5,7-dichloro-4-[2-(pyridyl)thiocarbonylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid benzyl ester

Intermediate 9 (3.7g) was dissolved in dry tetrahydrofuran (50ml). To this solution, triphenylphosphine (6.17g) and 2,2'-dithiopyridine (5.2g) were added and the reaction mixture was stirred for 1 h at room temperature under nitrogen atmosphere. The reaction mixture was diluted with ethyl acetate (200ml), then washed with HCl 1N (50ml), NaOH 2M (50ml) and brine (2x50ml). The organic layer was separated, dried, filtered and evaporated under vacuum. The crude product was purified by flash chromatography (EA/CH 3/7) to give the title compound (3.5g) as a yellow foam.

^{1}H -NMR(DMSO): 8.59 (m,1H); 7.78 (dt,1H); 7.62 (m, 2H); 7.45-7.27 (m, 5H); 6.84-6.76 (s, 3H); 5.15 (d, 1H); 4.97 (d, 1H); 4.40 (m, 1H); 3.92 (dd, 1H); 2.80 (m, 1H).

Intermediat 11

(+/-)-(E,E)-5.7-Dichloro-4-[4-(2-cyano-vinyl)-phenylcarbamoylmethylene]-1,2,3,4-terahydro-quinoline-2-carboxylic acid benzyl ester

Intermediate 7 (0.08g) was dissolved in acetonitrile (3 ml) and the solution deoxygenated with a flow of dry nitrogen for 5 min. Tetrakis (triphenylphosphine)palladium (0.021 g) was added and the heterogeneous mixture heated to 80°. After 3 h the mixture was cooled, diluted with ethyl acetate and washed twice with 3N HCl, then with water and brine. After drying and filtration the solution was concentrated to give a crude product, which was purified by column chromatography (CH/EA 7.5/2.5) to give the title compound (0.04 g) as a white solid.
mp: 146-148°C

NMR: ^{1}H d ($CDCl_3$) 10.42 (1H, bs), 7.71 (2H, d), 7.60 (2H, d), 7.57 (1H, d), 7.27 (1H, d), 7.23 (6H, m), 6.7 (2H, m), 6.32 (1H, d), 5.04 (1H, d), 4.86 (1H, d), 4.38 (1H, m), 4.24 (1H, dd) 2.81 (1H, dd).
IR: ($CDCl_3$) Vmax (cm^{-1}) 3375, 3325, 2216, 1730, 1717, 1616, 1589.

Intermediate 12
(+/-)(E,E)-4-[4-(2-tert-Butoxycarbonyl-vinyl)-phenylcarbamoylmethylene]-5,7-dichloro-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid benzyl ester

Intermediate 9 (0.10g) was dissolved in dry tetrahydrofuran (8.5ml) and the solution was cooled to -20°. At the same temperature PCl_5 (0.066g) was added and the reaction mixture was warmed to 0° and stirred for 1 h under nitrogen atmosphere. Pyridine (0.031ml) and 4-(4-nitro-phenyl)-but-3-enoic acid t-butyl ester (0.061g) were then added and the reaction mixture was stirred for 1 h at room temperature. The reaction mixture was then diluted with a saturated solution of NH_4Cl (5ml) and extracted with ethyl acetate (50ml), then the organic phase was washed with HCl 1 N (50ml), and with brine (50ml). The organic layer was separated, dried, filtered and evaporated under vacuum to give a crude product which was purified by flash chromatography (EA/CH 8:2) to give the title compound (0.10g) as a yellow solid mp 85°.

^{1}H NMR (DMSO): 10.34 (s, 1H); 7.69 (d 2H);7.49 (d, 2H); 7.48 (bs, 1H); 7.34 (d, 1H); 7.27 (d, 1H); 7.23 (m, 5H); 7.03 (bs, 1H); 6.73-6.71 (m, 3H); 6.50 (d, 1H); 5.05 (d, 1H); 4.85 (d, 1H); 4.4 (m, 1H); 4.25 (m, 1H); 2.80 (m, 1H).

Intermediate 13
(+/-)(E,E)-4-[4-(2-carbamoyl-vinyl)-phenylcarbamoylmethylene]-5,7-dichloro-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid benzyl ester

Intermediate 10 (0.3g) was dissolved in dry tetrahydrofuran (16ml). To this solution, 4-(4-amino-phenyl)but-3-enoic acid amide (0.029g) was added and the reaction mixture was refluxed for 36 h. The reaction mixture was diluted with ethyl acetate (8ml), then washed with HCl 3N (10ml), NaOH 5% (10ml) and brine (10ml). The organic layer was separated, dried, filtered and evaporated under vacuum. The crude product was purified by flash chromatography (EA) to give the title compound (0.035g) as a yellow solid m.p.>250°.

^{1}H NMR (DMSO): 10.12 (s, 1H); 7.55 (d, 2H); 7.24 (m, 5H); 7.10 (d, 2H); 6.85 (t, 1H); 6.70 (m, 3H); 5.04-4.84 (d, d, 2H); 4.35 (m, 1H); 4.25 (m, 1H); 3.10 (m, 2H); 2.79 (m, 1H); 2.62 (t, 2H); 1.34 (s, 9H).

IR (nujol): 3368, 3298, 1700, 1686.

Intermediate 14
(+/-)(E)-5,7-Dichloro-4-[4-(2-morpholin-4-yl-ethoxy)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid benzyl ester

Intermediate 10 (0.097g) was dissolved in dry toluene (10ml). To this solution, 4-[2-(4-morpholinyl)ethoxy]-benzeneamine (0.053g) was added and the reaction mixture was refluxed for 1 h. The reaction mixture was then cooled and a precipitate was formed which was filtered and triturated with isopropanol to give the title compound (0.075g) as a white solid.

^{1}H NMR (DMSO): 10.05 (s, 1H); 7.56 (d, 2H); 7.25 (m, 6H); 6.87 (d, 2H); 6.71 (d, 1H); 6.70 (d, 1H); 6.68 (s, 1H); 5.05 (d, 1H); 4.85 (d, 1H); 4.35 (m, 1H); 4.24 (dd, 1H); 4.03 (t, 2H); 3.57 (t, 4H); 2.8 (dd, 1H); 2.65 (t, 2H); 2.43 (m, 4H).

IR (nujol): 3335, 1722, 1643.

Intermediate 15

N-[2-(4-Nitro-phenoxy)-ethyl]-isobutyramide

2-(4-Nitro-phenoxy)ethylamine (0.27g) was dissolved in dry DCM (8.5ml) and dry pyridine (0.15ml) and isobutyryl chloride (0.12ml) were then added. After stirring for 1 h at room temperature, the reaction mixture was then diluted with HCl 3 N (50ml) and extracted with ethyl acetate (50ml), then the organic phase was washed with brine (50ml). The organic layer was separated, dried, filtered and evaporated under vacuum to give a crude product which was crystallized (diethyl ether, 7 ml) to give the title compound (0.11g) as a yellow solid. m.p. 102-103°.

^{1}H NMR ($CDCl_3$): 8.22 (d, 2H); 6.98 (d, 2H); 5.88 (bs, 1H); 4.15 (t, 2H); 3.72 (m, 2H); 2.39 (m, 1H); 1.18 (d, 6H); .

IR (nujol): 3319, 1647, 1593, 1340, 1175.

Intermediate 16

N-[2-(4-Amino-phenoxy)-ethyl]-isobutyramide

Intermediate 15 (0.19g) was dissolved in methanol (5ml) and Pd on carbon 5 % (0.19g) was then added. After stirring for 1 h 30 min at room temperature under hydrogen (1atm), the reaction mixture was filtered on Celite and evaporated under vacuum to give the title compound (0.15g) as a orange solid m.p. 99-100°.

^{1}H NMR ($CDCl_3$): 6.73 (m, 2H); 6.65 (m, 2H); 5.92 (bs, 1H); 3.96 (t, 2H); 3.62 (m, 2H); 3.46 (bs, 2H); 2.37 (m, 1H); 1.15 (d, 6H); .

IR (nujol): 3300, 1663.

Intermediate 17

(+/-)(E)-5,7-Dichloro-4-[4-(2-isobutyrylamino-ethoxy)-phenylcarbamoylmethylen]-1,2,3,4-tetrahydro-quin line-2-carboxylic acid b nzyl ester

Intermediate 10 (0.078g) was dissolved in dry toluene (8ml). To this solution, intermediate 16 (0.044g) was added and the reaction mixture was refluxed for 45 min. The reaction mixture was then cooled and a precipitate was formed which was filtered and triturated with isopropanol to give the title compound (0.080g) as a white solid.

^{1}H NMR (DMSO): 10.06 (s, 1H); 7.95 (t, 1H); 7.56 (d, 2H); 7.26-7.2 (m, 6H); 6.87 (d, 2H); 6.71 (d, 1H); 6.69 (d, 1H); 6.68 (s, 1H); 5.05 (d, 1H); 4.84 (d, 1H); 4.35 (m, 1H); 4.24 (dd, 1H); 3.92 (t, 2H); 3.36 (m, 2H); 2.80 (dd, 1H); 2.36 (m, 1H); 0.97 (d, 6H).

IR (nujol): 3315, 3292, 1722, 1649.

Intermediate 18

N-(4-t-butoxycarbonylamino-phenyl)-2-methoxy-acetamide

To a stirred solution of N-t-butoxycarbonyl-1,4-phenylene diamine (0.25g) in dry tetrahydrofuran (20ml) were added pyridine (0.12ml) and methoxyacetyl chloride (0.15g) and the reaction mixture was stirred for 1 hrs. The solution was diluted with ethyl acetate (50ml), washed with a 3N solution of hydrochloric acid (30ml) and brine (30ml), dried and concentrated in vacuum to give the title compound (0.35g). T.l.c. CH/EA acetate 1/1, R_f=0.33.

1H-NMR($CDCl_3$): 8.18(bs, 1H), 7.50(d, 2H), 7.32(d, 2H), 6.44(bs, 1H), 4.00(s, 2H), 3.49(s, 3H), 1.51(s, 9H).

Intermediate 19

N-(4-amino-phenyl)-2-methoxy-acetamide

A solution of intermediate 18 (0.35g) in dichloromethane/trifluoroacetic acid (10ml/10ml) was stirred for 2 hrs. The solvent was evaporated, the crude product was diluted with a 2N solution of sodium hydroxyde and extracted with ethyl acetate (4x50ml) and dichloromethane (50ml). The collected organic layers were dried and concentrated in vacuum. The crude product was purified by silica gel column chromatography using ethyl acetate as eluant to give the title compound (0.16g). T.l.c. ethyl acetate, R_f=0.43.

1H-NMR($CDCl_3$): 8.05(bs, 1H), 7.33(d, 2H), 6.66(d, 2H), 3.99(s, 2H), 3.60(bs, 2H), 3.49(s, 3H).

Intermediate 20

(+/-)(E)-5,7-dichloro-4-[4-(2-methoxy-acetylamino)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid, benzyl ester

To a stirred solution of intermediate 10 (0.12g) in dry toluene (10ml) was added intermediate 19 (0.053g) and the reaction mixture was heated at reflux for 2 hrs. The reaction mixture was cooled at 24°, affording a precipitate which was filtered to obtain the pure title compound (0.118g). T.l.c. ethyl acetate, R_f=0.75.

1H-NMR(DMSO): 10.15(bs, 1H), 9.64(bs, 1H), 7.58(m, 4H), 7.25(m, 6H), 6.72-6.70(m, 3H), 5.06(d, 1H), 4.85(d, 1H), 4.35(m, 1H), 4.25(dd, 1H)., 3.96(s, 2H), 3.35(s, 3H), 2.81(dd, 1H).

Intermediate 21

N-4(*tert*-Butoxycarbonylamino-phenyl)-2-benzyloxycarbonylamino-acetamide

To a solution of carbobenzyloxyglycine (0.6g) in acetonitrile (40ml) was added 1-hydroxybenzotriazole 90.4g), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.1g) and 4-(*tert*-butoxycarbonylamino) aniline (0.5g) and the reaction mixture was stirred at reflux for 5 hrs. After dilution with ethyl acetate, the solution was washed with 3 N hydrochloric acid, brine, 5% solution of sodium hydroxide and brine. The organic layer was dried, filtered and evaporated under vacuum to give a crude product which was triturated in diethyl ether (5ml) to give the title compound (0.54g) as a pale brown solid.

^{1}H NMR ($CDCl_3$): 7.79 (bs, 1H); 7.45-7.3 (m, 9H); 6.44 (bs, 1H); 5.43 (bs, 1H); 5.17 (s, 2H); 3.98 (d, 2H); 1.51 (s, 9H);
IR (nujol): 3439, 1724.

Intermediate 22

N-4(*tert*-Butoxycarbonylamino-phenyl)-2-amino-acetamide

A suspension of intermediate 21 (0.53g) in methanol (25ml) was hydrogenated at 1 atm for 1 hrs in the presence of 5% Pd/C (0.25g) as catalyst. The catalyst was filtered off on a paid of celite and the solution was evaporated to obtain the title compound (0.32g) as a pale pink solid.

^{1}H NMR (DMSO): 9.7 (bs, 1H); 9.22 (bs, 1H); 7.48 (d, 2H); 7.34 (d, 2H); 3.20 (s, 2H); 2.00 (b, 2H); 1.45 (s, 9H);
IR (nujol): 3314, 1732, 1645, 1603

Intermediate 23
N-4(*tert*-Butoxycarbonylamino-phenylcarbamoylmethyl)-isobutyramide

To a solution of intermediate 22 (0.32g) in THF (25ml) was added pyridine (0.19ml) and butyryl chloride (0.15ml) and the reaction mixture was stirred for 1 hrs. After dilution with ethyl acetate, the solution was washed with 3 N hydrochloric acid. The organic layer was dried, filtered and evaporated under vacuum to give a crude product which was triturated in diethyl ether (5ml) to give the title compound (0.31g) as a white solid.

^{1}H NMR (DMSO): 9.80 (s, 1H); 9.22 (s, 1H); 8.00 (t, 1H); 7.43 (d, 2H); 7.34 (d, 2H); 3.81 (d, 2H); 2.44 (m, 1H); 1.45 (s, 9H); 1.01 (d, 6H);
IR (nujol): 1724, 1705, 1634.

Intermediate 24
N-4(-amino-phenylcarbamoylmethyl)-isobutyramide

A solution of intermediate 23(0.31g) in dichloromethane/trifluoroacetic acid (6ml/6ml) was stirred for 1 hrs. The solution was evaporated and the residue was diluted with 5% solution of NaOH and extracted with ethyl acetate (4x50ml). The organic layer was dried, filtered and evaporated under vacuum to give a crude product which was purified by flash chromathography using ethyl acetate as to give the title compound (0.16g) as a brown foam.

^{1}H NMR (DMSO): 9.47 (s, 1H); 7.96 (t, 1H); 7.18 (d, 2H); 6.48 (d, 2H); 4.83 (bs, 2H); 3.77 (d, 2H); 2.44 (m, 1H); 1.00 (d, 6H);
IR (nujol): 3306, 1678, 1651.

Intermediate 25
(+/-)(E)-5,7-dichloro-4-(4-isobutyrrylaminomethylcarbonylamino-

ph nylcarbamoylm thylen)-1,2,3,4-tetrahydro-quinoline-2-carb xylic acid b nzyl st r

Intermediate 10 (0.53 g) was dissolved in toluene (50 ml). To this solution intermediate 24 (0.31 g) was added and the reaction mixture was stirred for 2 h at 110° The precipitated white solid was filtered and washed with ethyl ether (30 ml) to give the title compound (0.58 g) as a white solid.

^{1}H NMR (DMSO): 10.14 (s, 1H); 9.90 (s, 1H); 8.04 (t, 1H); 7.58 (d, 2H); 7.49 (d, 2H); 7.25 (m, 5H); 6.72 (d, 1H); 6.70 (d, 1H); 6.70 (s, 1H); 5.05 (d, 1H); 4.86 (d, 1H); 4.36 (m, 1H); 4.25 (dd, 1H); 3.83 (d, 2H); 2.82 (dd, 1H); 2.46 (m, 1H); 1.01 (d, 6H).
IR (nujol):1717, 1643, 3281.

Example 1

(+/-)-(E,E)-5.7-Dichloro-4-[4-(2-cyano-vinyl)-phenylcarbamoylmethylene]-1,2,3,4-terahydro-quinoline-2-carboxylic acid

Intermediate 11 (0.032 g) was dissolved in 95% ethanol (4 ml) and water (1 ml) and treated at room temperature for 1 h with LiOH (0.005 g). The solution was then concentrated and the resulting solid was triturated with 3N HCl (2 ml) for 1 h. Filtration of the suspension yielded the title compound (0.025 g) as a yellow solid **mp:** >200°.

NMR: ^{1}H d ($CDCl_3$) 12.73 (1H, bs), 10.39 (1H, bs), 7.70 (2H, d), 7.60 (2H, d), 7.56 (1H, d), 7.22 (1H, s), 7.15 (1H, d), 6.70 (1H, d), 6.68 (1H, d), 6.31 (1H, d), 4.13 (1H, td), 3.90 (1H, dd), 3.03 (1H, dd).
IR: ($CDCl_3$) Vmax (cm^{-1}) 3321, 2286, 1770, 1690.

Example 2

(+/-)(E,E)-4-[4-(2-tert-Butoxycarbonyl-vinyl)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid

Intermediate 12 (0.046g) was suspended in ethanol (5ml) and water (2ml). To this solution $LiOH(H_2O)$ (0.007g) was added and the reaction mixture was stirred for 0.5 h at room temperature until a clear pale yellow solution was obtained. HCl 2 N (5ml) was then added dropwise and the resulting acidic solution diluted with ethyl acetate (10ml); The organic layer was separated, dried and evaporated under vacuum. The crude product was triturated with diethyl ether (3ml) and petrolium ether (3ml).The

precipitate was filtered, washed with small amounts of petrolium ether and dried to give the title compound (0.015g) as a yellow solid m.p.140°

^{1}H NMR (DMSO): 12.84 (bs, 1H); 10.40 (bs, 1H); 7.68 (d, 2H); 7.62 (d, 2H); 7.61 (d, 1H); 7.15 (bs, 1H); 6.70 (m, 3H); 6.40 (d, 1H); 4.13 (m, 1H); 3.94 (dd, 1H); 3.01 (dd, 1H); 1.47 (d, 9H).

Example 3

(+/-)(E,E)-4-[4-(2-carbamoyl-vinyl)-phenylcarbamoylmethylene]-5,7-dichloro-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid

Intermediate 13 (0.098g) was suspended in ethanol (5ml) and water (2.5ml). To this solution LiOH.(H_2O) (0.006g) was added and the reaction mixture was stirred for 2 h at room temperature until a clear pale yellow solution was obtained. HCl 2 N (5ml) was then added dropwise and the resulting acidic solution diluted with water (10ml); the precipitate thus formed was filtered, washed with small amounts of cold water and dried to give the title compound (0.020g) as a white solid m.p > 250°.

^{1}H NMR (DMSO): 12.71 (bs, 1H); 10.30 (bs, 1H); 7.67 (d, 2H); 7.49 (d, 2H); 7.46 (bs, 1H); 7.01 (bs, 1H); 7.34 (d, 1H); 7.14 (db, 1H); 6.70 (m, 1H); 6.69 (d, 1H); 6.68 (d, 1H) 4.12 (m, 1H); 3.90 (dd, 1H); 3.03 (dd, 1H) m.p >250°.

IR (nujol): 3310, 3420, 1710, 1657, 1610.

Example 4

(+/-)(E)-5,7-dichloro-4-[4-(2-morpholin-4-yl-ethoxy)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid

Intermediate 14 (0.049g) was suspended in ethanol (9ml) and water (3ml). To this solution LiOH(H_2O) (0.014g) was added and the reaction mixture was stirred for 0.5 h at room temperature until a clear pale yellow solution was obtained. HCl 3 N (5ml) was then added dropwise until pH=3 and the resulting acidic solution diluted with ethyl ac tate (50ml) and water (50 ml); The organic layer was s parated, dried and

evaporated under vacuum. The crude product was triturated with water (2ml) and with diethyl ether / EA (1 / 1) to give the title compound (0.027 g) as a yellow solid.

^{1}H NMR (DMSO): 12.67 (bs, 1H); 10.10 (s, 1H); 7.55 (d, 2H); 7.13 (d, 1H); 6.87 (d, 2H); 6.70 (d, 1H); 6.67 (s, 1H); 6.65 (d, 1H); 4.10-4.04 (m, 3H); 3.85 (m, 1H); 3.57 (m, 4H); 3.05 (dd, 1H); 2.6 (m, 2H); 2.4 (m, 4H).

IR (nujol): 3387.

Example 5
(+/-)(E)-5,7-dichloro-4-(4-cyanomethyl-phenylcarbamoylmethylene)-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid

4-Cyanomethylaniline (0.081g), was added to a solution of intermediate 10 (0.2g) dissolved in dry toluene (10ml) and dry tetrahydrofuran (10ml). The reaction mixture was stirred for 3 h at 110 °C and then diluted with ethyl acetate (50ml), washed with a saturated aqueous solution of NH_4Cl (50ml) and with brine (50ml). The organic layer was separated, dried, filtered and evaporated under vacuum to give a crude product which was triturated in ethyl acetate (5ml) and petroleum ether (20ml). The yellow solid thus obtained (0.140g), was dissolved in ethanol (20ml) and water (5ml). To this solution, $LiOH(H_2O)$ (0.023g) was added and the reaction mixture was stirred for 1 h at room temperature. HCl 2 N (5ml) was then added dropwise and the resulting acidic solution diluted with water (30ml); the precipitate thus formed was filtered, washed with small amounts of cold water and dried to give the title compound (0.057g) as a yellow solid m. p.: 200-202 °C.

^{1}H (DMSO): 12.7 (bs, 1H); 10.2 (s, 1H); 7.65 (d, 2H); 7.27 (d, 2H); 6.7-6.67 (m, 3H); 4.11 (m, 1H); 3.96 (s, 2H); 3.89 (dd, 1H); 3.05 (dd, 1H).

IR (nujol): 3366; 3321; 2270; 1728.

Example 6
(+/-)(E)-5,7-Dichloro-4-[4-(2-isobutyrylamino-ethoxy)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid

Intermediate 17 (0.066g) was suspended in ethanol (9ml) and water (3ml). To this solution LiOH.(H_2O) (0.019g) was added and the reaction mixture was stirred for 1 h at room temperature until a clear pale yellow solution was obtained. After evaporation of the solvent, HCl 1 N was then added dropwise until pH = 1 and the resulting acidic solution diluted with water (30ml); the precipitate thus formed was filtered, washed with small amounts of cold water, triturated with isopropanol (2ml) and dried to give the title compound (0.029g) as a white solid.

^{1}H NMR (DMSO): 12.70 (s, 1H); 10.01 (s, 1H); 7.95 (t, 1H); 7.54 (d, 2H); 7.10 (d, 1H); 6.87 (d, 2H); 6.69 (d, 1H); 6.67 (d, 1H); 6.66 (bs, 1H); 4.10 (m, 1H); 3.92 (t, 2H); 3.88 (dd, 1H); 3.36 (m, 2H); 3.05 (dd, 1H); 2.36 (m, 1H); 0.97 (d, 6H).

IR (nujol): 3333, 1726, 1650, 1628.

Example 7
(+/-)(E)-5,7-dichloro-4-[4-(2-methoxy-acetylamino)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid

To a stirred solution of intermediate 20 (0.06g) in ethanol/water (6ml/2ml), was added lithium hydroxide monohydrate (0.018g) and the reaction mixture was stirred for 1 hrs. The solution was evaporated, then diluted with a 3N solution of hydrochloric acid (5ml). The formed precipitate was filtered, washed with water and triturated in acetonitrile (2ml) to give the title compound (0.034g).

1H-NMR(DMSO): 12.72(s, 1H), 10.11(s, 1H), 9.68(s, 1H), 7.57(m, 4H), 7.11(d, 1H), 6.69(d, 1H), 6.68(s, 1H), 6.67(d, 1H), 4.11(m, 1H), 3.96(s, 2H)., 3.9(dd, 1H), 3.36(s, 3H), 3.06(dd, 1H).

Example 8
(+/-)(E)E-5,7-dichloro-4-[4-(2-cyano-vinyl)phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid sodium salt

Example 1 (0.040g) was suspended in water (5ml) and methanol (1ml). NaOH 1 M (0.093ml) was then added and the reaction mixture was stirred for 10' at room temperature until a clear pale yellow solution was obtained. The resulting solution was then freeze-dried for 32 h to giv the title compound (0.033g) as a yellow solid.

^{1}H NMR (DMSO): 11.86 (bs, 1H); 7.60 (d, 2H); 7.55 (d, 1H); 7.32 (d, 2H); 6.78 (d, 1H); 6.74 (d, 1H); 6.54 (m, 1H); 6.50 (d, 1H); 6.32 (d, 1H); 3.52 (m, 1H); 3.16 (m, 1H); 2.73 (m, 1H).

IR (nujol): 3326-2670, 2218, 1664, 1600.

Example 9
(+/-)(E)-5,7-dichloro-4-(4-isobutyrylaminomethylcarbonylamino-phenylcarbamoylmethylene)-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid sodium salt

Intermediate 25 (0.58 g) was suspended in ethanol/methanol solution (95:5 respectively) (0.81ml). NaOH 1N (0.93 ml) was added and the solution was stirred 1 h at RT. The solution becomes clear yellow. Ethyl acetate (100 ml) and diethyl ether (50 ml) were in turn added dropwise and the precipitated yellow solid filtered and dried to give the title compound (0.44 g) as a yellow solid.

^{1}H NMR (DMSO): 11.19 (bs, 1H); 9.99 (bs, 1H); 8.17 (t, 1H); 7.66 (m, 2H); 7.50 (m, 2H); 6.75-6.69 (d+bs, 2H); 6.53-6.50 (s+d, 2H); 3.83 (d, 2H); 3.50-3.41 (m+dd, 2H); 2.58-2.45 (dd+m, 2H); 1.01 (d, 6H).

IR (nujol): 3294, 1691, 1653.

Pharmacy Example

Intravenous Infusion	**% w/v**
A glycine antagonist of formula (I)	0.3 - 0.5
Polysorbate 80	1
tris(hydroxymethyl)aminomethane	0.54
Dextrose solution 5% w/v	qs to volume

Intravenous injection	
A glycine antagonist of formula (I)	0.3 - 3

Polysorbate 80	1
tris(hydroxymethyl)aminomethane	0.54
Dextrose solution 5% w/v	qs to volume

The glycine antagonist and Polysorbate were added to a solution of tris(hydroxymethyl)aminomethane in a 5% aqueous dextrose solution suitable for injection. The solution was filtered through a sterile 0.2 micron sterlising filter and filled in containers before being sterilised by autoclaving.

The affinity of a compound of the invention for strychnine insensitive glycine binding site located on the NMDA receptor complex was determined using the procedure of Kishimoto H. et al J. Neurochem 1981, 37, 1015-1024. The pKi values obtained with representative compounds of the invention are given in the following table.

Example No.	pKi
3	8.1
4	7.2
5	8.1
6	7.8
7	8.2
9	8.1

The ability of compounds of the invention to inhibit NMDA induced convulsions in the mouse was determined using the procedure of Chiamulera C et al. Psychopharmacology 1990, 102, 551-552. In this test the ability of the compound when administered iv to inhibit the generalized seizures induced by an intracerebroventricular injection of NMDA in mice was examined at 0.1 mg/kgdose .

The results as percent (%) of inhibition at 0.1 mg/kg dose for representative compounds are given below:

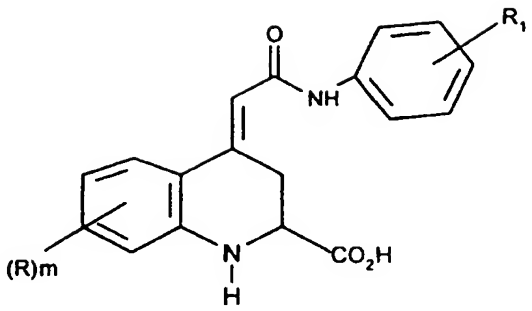
Ex No.	% of inhibition

7	40%
9	40%
6	40%
3	40%

No untoward effects have been observed when compounds of the invention have been administered to mice (either i.v. or po) at pharmacologically active doses.

Claims

1. A compound of formula (I)



(I)

a salt, or a metabolically labile ester thereof wherein R represents a group selected from halogen, alkyl, alkoxy, amino, alkylamino, dialkylamino, hydroxy, trifluoromethyl, trifluoromethoxy, nitro, cyano, SO_2R_2or COR_2 wherein R_2 represents hydroxy, methoxy, amino, alkylamino or dialkylamino; m is zero or an integer 1 or 2;

R_1 represents a group (CH_2)nCN, -CH=CHR_3, (CH_2)nNHCOCH_2R_4 or O(CH_2)pNR_5R_6; R_3 represents cyano or the group COR_7;

R_4 represents alkoxy or a group $NHCOR_8$;

R_5 and R_6 each represent independently hydrogen or alkyl, or

R_5 and R_6 together with the nitrogen atom to which they are attached represent a heterocyclic group, or R_5 is hydrogen and R_6 is the group COR_9;

R_7 represents an alkoxy, amino or hydroxyl group;

R_8 represents a hydrogen atom or optionally substituted alkyl, alkoxy, phenyl, heteroaryl or heterocyclic group;

R_9 is the group R_8 or the group $NR_{10}R_{11}$ wherein

R_{10} represents hydrogen or alkyl group;

R_{11} represents optionally substituted alkyl, phenyl, heteroaryl , heterocyclic or cycloalkyl group;

n is zero or an integer from 1 to 4; p is an integer from 2 to 4.

2. A compound of formula(I) as claimed in claim 1, a physiologically acceptable salt or a metabolically labile ester ther of.

3. A compound of formula(I) as claimed in claim 1 or 2 wherein m is 1 or 2, and R is halogen atom in the 5 and /or 7 position.

4. A compound of formula(I) as claimed in any of claims 1 to 3 wherein m is 2 and R is chlorine in the 5 and 7 position.

5. A compound of formula(I) as claimed in any of claims 1 to 4 wherein R_1 is the group $(CH_2)nCN$, - $CH=CHR_3$, wherein R_3 is cyano or COR_7, in which R_7 is C_{1-4} alkoxy, amino, $(CH_2)nNHCOCH_2R_4$ wherein R_4 is C_{1-4} alkoxy, $NHCOR_8$ wherein R_8 is hydrogen or C_{1-4}alkyl ,$O(CH_2)pNR_5R_6$ wherein R_5 and R_6 are hydrogen or NR_5R_6 represents morpholino or R_5 represents hydrogen and R_6 is COR_9 wherein R_9 is hydrogen or C_{1-4}alkyl, n is zero, 1 or 2; p is 2, 3 or 4

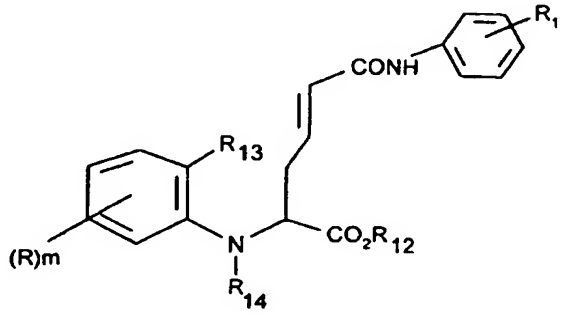
6 A compound of formula (I) as claimed in claim 5 wherein R_1 is the group cyanomethyl , $CH=CHR_3$, wherein R_3 is a t-butoxycarbonyl, carbamoyl,cyano group, 2-isobutyrylamino-ethoxy, 2-methoxy-acetylamino, isobutirrylamino methylcarbonylamino, 2-morpoholin-4yl-ethoxy.

7 A compound selected from
(±) (E) 5,7- Dichloro- 4-[4-(2-methoxy-acetylamino)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
(±) (E) 5,7- Dichloro- 4-[4-(2-isobutyrylamino-methylcarbonylamino)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
(±) (E) 5,7- Dichloro- 4-(4-cyanomethyl-phenylcarbamoylmethylene)-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
(±) (E,E) 5,7- Dichloro- 4-[4-(2-cyano-vinyl)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
(±) (E,E) 4-[4-(2-tert-butoxycarbonyl-vinyl)-phenylcarbamoylmethylene]-5,7-dichloro-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
(±) (E,E) 4-[4-(2-carbamoyl-vinyl)-phenylcarbamoylmethylene]-5,7- dichloro-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
(±) (E) 5,7- Dichloro- 4-[4-(2-isobutyrylamino-ethoxy)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;
(±) (E) 5,7- Dichloro- 4-[4-(2-morpholin-4-yl-ethoxy)-phenylcarbamoylmethylene]-1,2,3,4-tetrahydro-quinoline-2-carboxylic acid;

and physiologically acceptable salts e.g. sodium salt , metabolically labile esters or enantiomers thereof.

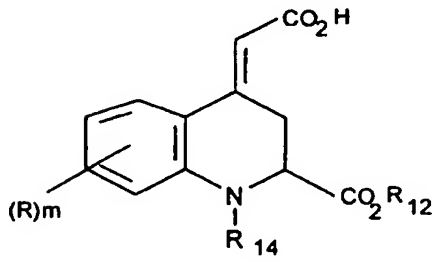
8. A process for the preparation of compounds of claim 1 or claim 2 which comprises:

(a) cyclisation of a compound of formula (II)

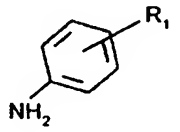


(II)

(b) reacting an activated derivative of the carboxylic acid (III)



(III)



(IV)

followed where necessary or desired by one or more of the following steps:-

1. removal of the carboxyl protecting group;
2. isolation of the compound of formula (I) as a salt thereof;
3. separation of a compound of formula (1) into a specific enantiomer thereof.

9. A pharmaceutical composition comprising a compound as claimed in any of claims 2 to 7 in admixture with one or more physiologically acceptable carriers or excipients.

10 , The use of a compound as claimed in any of the claims 2 to 7 in the manufacture of a medicament for antagonising the effects of excitatory amino acids upon the NMDA receptor complex.

11. Compounds as claimed in any of the claims 2 to 7 for use in therapy.

12. A method of treatment of a mammal including man for conditions where antagonising the effects of excitatory amino acids on the NMDA receptor complex is of therapeutic benefit comprising administration of a compound as claimed in any of claims 2 to 7

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 97/04440

A. CLASSIFICATION OF SUBJECT MATTER
IPC 6 C07D215/48 A61K31/47

According to International Patent Classification(IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 6 C07D

Documentation searched other than minimumdocumentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	R.W. CARLING ET AL.: "Anticonvulsant activity of glycine-site NMDA antagonists." BIOORGANIC & MEDICINAL CHEMISTRY LETTERS, vol. 3, no. 1, 1993, pages 65-70, XP000610559 cited in the application see the whole document ---	1-12
A	EP 0 386 839 A (MERCK SHARP & DOHME) 12 September 1990 cited in the application see claims ---	1-12
P,X	WO 97 12870 A (GLAXO WELLCOME SPA ;FABIO ROMANO DI (IT); GIACOBBE SIMONE (IT); BE) 10 April 1997 see claim 1 -----	1-12

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

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Date of the actual completion of theinternational search	Date of mailing of the international search report
27 January 1998	06. 02. 98

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	De Jong, B

Form PCT/ISA/210 (second sheet) (July 1992)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 97/ 04440

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.: 12
because they relate to subject matter not required to be searched by this Authority, namely:
Although claim 12 is directed to a method of treatment of the animal/human body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [ ] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/EP 97/04440

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0386839 A	12-09-90	AT 147732 T	15-02-97
		AU 5114490 A	13-09-90
		CA 2011686 A	08-09-90
		DE 69029668 D	27-02-97
		DE 69029668 T	07-08-97
		JP 3034969 A	14-02-91
		US 5231102 A	27-07-93
WO 9712870 A	10-04-97	AU 7214896 A	28-04-97